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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,340	08/01/2003	Cornelia J. Forster	VPI/02-119 US	3588
27916	7590	03/10/2006	EXAMINER	
VERTEX PHARMACEUTICALS INC. 130 WAVERLY STREET CAMBRIDGE, MA 02139-4242			BALASUBRAMANIAN, VENKATARAMAN	
			ART UNIT	PAPER NUMBER

1624

DATE MAILED: 03/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/632,340

Applicant(s)

FORSTER ET AL.

Examiner

Venkataraman Balasubramanian

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 December 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15, 18 and 23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-15, 18 and 23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/20/2005 has been entered.

Applicants' response, which included amendment to claims 18 and 23 along with cancellation of claims 16, 17 and 19-22, is also acknowledged.

Claims 1-15, 18 and 23 are now pending.

In view of applicants' response, the 112 first paragraph rejection over claims 17-23 now applicable to claims 18 and 23 have been obviated. However, the following rejections apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating leukemia does not reasonably provide enablement for treatment any or all diseases or conditions including those yet to be linked with the various mode of action embraced in the claim language. The

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specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claim 14 is drawn to pharmaceutical composition with intended method of use to treat various diseases such Alzheimer's disease, Parkinson disease, multiple sclerosis, asthma, inflammation, stroke, immunosuppression cardiovascular disease, depression, psychosis etc., "which as recited reads on any or all diseases or conditions for which there is no enabling disclosure. The scope of the claims includes treatment of various diseases or conditions, which are not adequately enabled solely based on the activity of the compounds, provided in the specification. The instant compounds are disclosed have GSK-3 kinase phosphorylation inhibitory activity and it is recited that the instant compounds are useful in treating any or all diseases for which applicants provide no competent evidence. Reading specification it appears that instant compound is useful for treating all sorts of diseases including autoimmune diseases, neurodegenerative diseases or disorders, all inflammatory diseases, all metabolic disorders, all psychiatric disorders, all cardiovascular diseases, etc. for which applicants have not provided any experimental support or nexus. Prior art searches do not lend support to, except for treating leukemia treatments of all diseases embraced in the claim language. That a single class of compounds can treat all or any disease /disorder is an incredible finding for which applicants have not provided enabling disclosure and prior art search at the time of instant invention suggest the use of these inhibitors is still under experimental stage and speculative in nature. Furthermore, the applicants have

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not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Moreover many if not most of diseases such as Alzheimer's disease, multiple sclerosis, ALS, bipolar disorder etc. are very difficult to treat and at present there is no known drug, which can successfully lessen the course of these diseases, despite the fact that there are many drugs, which can be used for "inflammatory condition".

Inflammation itself is a complex process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

The "autoimmune diseases" are a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are hundreds such diseases, which have fundamentally different mechanisms and different underlying causes. Thus, the scope of claims is extremely broad.

No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this

revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of pathology of diseases and disorders.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See *Ex parte Jovanovics*, 211 USPQ 907, 909; *In re Langer* 183 USPQ 288. Also note *Hoffman v. Klaus* 9 USPQ 2d 1657 and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The state of the art is indicative of the requirement for undue experimentation. See *Duhe et al.* *Cell Biochem. Biophys.* 34(1): 17-59, 2001, *Rane et al.*, *Oncogene* 19(49): 5662-79, 2000, and *Kim et al.*, *Curr. Opin Genet Dev.* 10(5): 508-514, 2000 (PubMed Abstracts provided)

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic uses of the compounds in treating several diseases of that require GSK-3 kinase inhibitory activity.

2) The state of the prior art: Recent publications at the time of instant invention suggest that GSK-3 kinase as therapeutic agents is still in experimental stage. See references cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for the therapeutic effect of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show therapeutic effect and the state of the art is that the effects GSK-3 kinase inhibitors are still in experimental stage

6) The breadth of the claims: The instant claims embrace treatment of several diseases including those yet to be related to GSK-3 kinase activity.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature

of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

This rejection is same as made in the previous office action. And is now limited to claim 14 with the intended use for treating various diseases. It should be noted that this rejection was previously applied to claims 17-23 along with claim 14. To obviate this rejection applicants have amended claims 18 and 23 and have cancelled claim 17 and 19-22. But applicants have not addressed the issue as applied to claim 14.

Hence this rejection is proper and is maintained.

Claim 15 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting GSK-3 activity in a standard biological assay, does not reasonably provide enablement for a method of

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inhibiting GSK-3 activity in a biological sample generally for the purpose of blood transfusion, organ transplantation, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim is drawn to ‘a method of inhibiting GSK-3 activity in a biological sample’ and the term “biological sample” as per the definition in the specification (page 21, lines 11-134 “includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof”).

First, the instant claim 15 is a ‘reach through’ claim. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through to the corresponding therapeutic method of any or all diseases, disorders or conditions, for which they lack written description and enabling

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disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

As can be seen from the definition of the term "biological sample", without limitation it reads on many and all types of biological samples, which can include mammals or animals and therefore, the claimed method is seen to encompass an inhibitory method wherein the compound is administered to an animal. This is further evident from the purpose of the inhibition of GSK-3 activity stated in pages 21, lines 11-18, which includes for example, blood transfusion, organ-transplantation, etc. As the inhibition of GSK-3 activity in a biological sample is disclosed to be useful for blood transfusion, organ-transplantation, etc., it implicitly reads on the inherent therapeutic methods characterized by the activity, which as per the specification includes numerous types of diseases/disorders recited in page 20

The sole testing assay provided in the specification at page 32 is to test the ability of the compounds to inhibit GSK-3 β activity using a standard coupled enzyme system, however, there is insufficient guidance in the disclosure regarding the provided assay. First, the specification provides that the coupled enzyme system is provided in Fox et al., however, the cited article deals with inhibition of p38 MAP kinase activity. Next, applicant has not provided how this correlates with the efficacy in all types of biological samples encompassed by the instant method and their use in the various purposes wherein the inhibition activity is useful. For example, blood transfusion is the process of transferring blood or blood-based products from one person into the circulatory system of another. Blood transfusions may be seen as a procedure to treat

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some medical conditions, such as massive blood loss due to trauma, surgery, shock and where the red cell producing mechanism (or some other normal and essential component) fails. Similarly, an organ transplantation is the transplantation of a whole or partial organ from one body to another (or from a donor site on the patient's own body), for the purpose of replacing the recipient's damaged or failing organ with a working one from the donor site. As can be seen from the above, without limitation these purposes are intended for therapeutic methods and applicant has not provided competent evidence sufficient to enable the claimed method.

Further, the instantly claimed method alternatively recites the use of 'a pharmaceutical composition comprising the compound of formula I and a pharmaceutically acceptable carrier, adjuvant or vehicle' as being added to the biological sample, see the last three lines of the claim. A pharmaceutical composition of the kind recited in the instant claims is generally used for internal administration type therapeutic methods. Therefore, the instant claim appears to be directed to the various types of therapeutic methods associated with GSK-3 inhibition activity.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-15, 18 and 23 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,696,452. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter embraced in the instant claims is an obvious variant of the subject matter taught in the claims of US 6,696,452. Note when R^x is hydrogen, R² and R^{2'} form a benzo ring or pyridine ring with C-ring as

substituted phenyl and R^y an optionally substituted aliphatic group, the compounds, composition and the method of use with same mode of action taught by US 6,696,452 overlap with the instant claims 1-15. Note the complex composition claim 14 is also included in this rejection as it is obvious based on the teachings of US 6,696,452.

This rejection is same as made in the previous office action except that the cancelled claims are excluded from this rejection. Applicants' have differed addressing the issue.

Hence, this rejection is maintained.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you

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have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

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3/4/2006